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09/381,480	12/10/1999	MARK CHEE	018547-03053	4017

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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1655	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/381,480	Chee
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- **The MAILING DATE of this communication appears on the cover sheet with the correspondence address** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Nov 29, 2001 .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-15 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Application/Control Number: 09/381,480

Art Unit: 1655

DETAILED ACTION

Specification

1. In response to the interview with the applicant on August 23, 2001, the previous rejections are hereby withdrawn and substituted by new supplemental office action. The new office action is as follows.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-2, 5-6 and 15 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent 5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000).

Skiena teaches a method of analyzing a target nucleic acid (abstract), comprising:

a) designing an array of probes comprising a probe set comprising probes complementary to a reference sequence (Abstract, Table 1 and Column 2, lines 20-27 and Claim 1a);

b) hybridizing the target nucleic acid to the array of probes (Claim 1b);

c) determining the relative hybridization of the probes to the target nucleic acid (Claim 1c);

d) estimating the sequence of the target nucleic acid from the relative hybridization of the probe (Claim 1c and 1d);

e) providing a further array of probes comprising a probe set comprising probes complementary to the estimated sequence of the target nucleic acid (Claim 1d and 1e);

f) hybridizing the target nucleic acid to the further array of probes (Claim 1g);

g) determining the relative hybridization of the probes to the target nucleic acid (Claim 1g);

h) reestimating the sequence of the target nucleic acid from the relative hybridization of the probes (Claim 1h and Claim 2).

Skiena teaches a method further comprising repeating steps (e)-(h) as necessary until the reestimated sequence of the target nucleic acid is constant between successive cycles (Claim 2).

Skiena teaches a method of analyzing a target nucleic acid by designing an array of probes to be complementary to an estimated sequence of the target nucleic acid (Figures 2-3 and Claims 3-14).

Skiena does not teach the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence.

Futreal et al. teach the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence (Abstract, Figures 1, 2 and 4 and Column 10, lines 23-37).

Skiena does not teach a method wherein the target nucleic acid shows 50-99% sequence identity with the reference sequence.

Futreal et al. teach a method wherein the target nucleic acid shows 50-99% sequence identity with the reference sequence. (Figures 1, 2 and 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence of Futreal et al. in the method of

Skiena since Futreal et al. state, "Such oligonucleotide probes or primers, as well as the full length sequence (and alleles, variants and derivatives) are also useful in screening a test sample containing a nucleic acid for the presence of alleles and variants, especially those that confer susceptibility or predisposition to cancers, the probes hybridizing with a target sequence from a sample obtained from the individual being tested. The conditions of the hybridization can be controlled to minimize non-specific binding, and preferably stringent to moderately stringent hybridization conditions are preferred. The skilled person is readily able to design such probes, label them and devise suitable conditions for hybridization reactions, assisted by textbooks such as Sambrook et al and ausubel et al. As well as determining the presence of polymorphisms or mutations in the BRCA2 sequence, the probes may also be used to determine whether mRNA encoding BRCA2 is present in a cell or tissue (Column 9, lines 4-21)." An ordinary practitioner would have been motivated to combine and substitute the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence of Futreal et al. in the method of Skiena in order to achieve the express advantages noted by Futreal et al. of probes which skilled person is readily able to design, label them and devise suitable conditions for hybridization reactions, assisted by textbooks such as Sambrook et al and ausubel et al., and which oligonucleotide probes or primers, as well as the full length sequence (and alleles, variants and derivatives) are also useful in screening a test sample containing a nucleic acid for the presence of alleles and variants, especially those that confer susceptibility or predisposition to cancers, the probes hybridizing with a target sequence from a sample obtained from the individual being tested.

4. Claims 1-2 and 5-15 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent 5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000)

further in view of Cronin et al. (U.S. Patent 6,027,880) (February 22, 2000)

Skiena in view of Futreal et al. teach methods of claims 1-2, 5-6 and 15 as described above.

Skiena in view of Futreal et al. do not teach a method wherein the reference sequence is 10 Kb nucleotides long, the array comprises a probe set comprising overlapping probes that are perfectly complementary to and span the reference sequence, and the further array comprises probes that are perfectly complementary to and span the estimated sequence.

Cronin et al. teach a method wherein the reference sequence is 10 Kb nucleotides long, the array comprises a probe set comprising overlapping probes that are perfectly complementary to and span the reference sequence, and the further array comprises probes that are perfectly complementary to and span the estimated sequence (Table 3, columns 63 and 64, Mutation Number 3849).

Skiena in view of Futreal et al. do not teach a method wherein the reference sequence includes at least 90% of the human genome.

Cronin et al. teach a method wherein the reference sequence includes at least 90% of the human genome (Column 42, lines 15-25).

Skiena in view of Futreal et al. do not teach a method wherein the array of probes comprises:

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least six nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence;

(2) second, third and fourth probe sets, each comprising a corresponding probe for each

probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least six nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

Cronin et al. teach a method wherein the array of probes comprises:

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least six nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence (Figure 3),

(2) second, third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least six nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets (Figures 3, 7, 8 and 9 and Claim 28).

Skiena in view of Futreal et al. do not teach a method wherein the sequence of the target nucleic acid is estimated by :

a) comparing the relative specific binding of four corresponding probes from the first, second, third and fourth probe sets ;

b) assigning a nucleotide in the sequence of the target nucleic acid as the complement of the interrogation position of the probe having the greatest specific binding ;

Cronin et al. teach a method wherein the sequence of the target nucleic acid is estimated

by :

a) comparing the relative specific binding of four corresponding probes from the first, second, third and fourth probe sets (Column 164, claim 28, lines 51-53);

b) assigning a nucleotide in the sequence of the target nucleic acid as the complement of the interrogation position of the probe having the greatest specific binding (Column 164, claim 28, lines 54-56);

Skiena in view of Futreal et al. do not teach a method wherein the sequence of the target nucleic acid differs from the reference by at least two positions within a probe length.

Cronin et al. teach a method wherein the sequence of the target nucleic acid differs from the reference by at least two positions within a probe length (Column 35, lines 1-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the sequencing of whole human genome study of Cronin et al. in the method of Skiena in view of Futreal et al., since Cronin et al. state, "The invention provides several strategies employing immobilized arrays of probes for comparing a reference sequence of known sequence with a target sequence showing substantial similarity with the reference sequence, but differing in the presence of , e.g., mutations (Column 2, lines 8-12)." An ordinary practitioner would have been motivated to combine and substitute the sequencing of whole human genome study of Cronin et al. in the method of Skiena in view of Futreal et al. in order to achieve the express advantages noted by Cronin et al. of a method which provides several strategies employing immobilized arrays of probes for comparing a reference sequence of known sequence with a target sequence showing substantial similarity with the reference sequence, but differing in the presence of , e.g., mutations.

5. Claims 1-6 and 15 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent

5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000) further in view of Horwitz et al. (Journal of Virology, (1992), Vol. 66 (4), pages 2170-2179).

Skiena in view of Futreal et al. teach method of claims 1, 2, 5-6 and 15 and as described above.

Skiena in view of Futreal et al. do not teach method wherein the target nucleic acid sequence is a species variant of the reference sequence and wherein the reference sequence is from a human and the target nucleic acid is from a primate.

Horwitz et al teach method wherein the target nucleic acid sequence is a species variant of the reference sequence and wherein the reference sequence is from a human and the target nucleic acid is from a primate (Abstract and Figures 1 and 3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to include the comparative primate versus human gene sequence study of Horwitz et al. in the method of Skiena in view of Futreal et al., since Horwitz et al. state, "Because of the recent identification of several classes of human endogenous retroviruses and our interest in obtaining a better understanding of the evolution of human immunodeficiency virus (HIV), experiments were performed to detect the presence of HIV-1 related sequences in normal human DNA (Page 2170, column 2, second paragraph, lines 1-6)." An ordinary practitioner would have been motivated to combine the comparative primate versus human gene sequence study of Horwitz et al. in the method of Skiena in view of Futreal et al. in order to achieve the express advantages noted by Horwitz et al. of obtaining a better understanding of the evolution of human immunodeficiency virus (HIV).

Response to Arguments

6. Applicant's arguments filed on November 29, 2001 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that Skiena reference does not teach array of probes designed with respect to a reference sequence. This argument is not persuasive. It has been clearly mentioned in the last office action that Futreal reference teaches array of probes designed with respect to a reference sequence.

Applicant argues that Skiena reference does not teach the "estimating" of a sequence of the claimed invention. Applicant argues that the word "estimating" was not found in Skiena reference and only the word "identifying" is found. Applicant argues that because Skiena has a preferred embodiment of "estimating", Skiena is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Skiena has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Skiena

reference uses the word "identifying", the property of "estimating" a nucleotide sequence is inherently present in this chemically and structurally identical molecule. For example, Skiena teaches that such estimation can be done by resolving ambiguities in sequences of target nucleic acids ((Column 3, line 1 to Column 4, line 32). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any identification of nucleic acids under any suitable conditions can be used for estimating the sequence of nucleic acids.

Therefore, all the rejections made in the last office action are hereby maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL in view of the response to argument.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing

date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

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Arun Chakrabarti

Patent Examiner

Art Unit 1655

December 3, 2001